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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/003,669 | 11/01/2001 | Robert H. Broyles | 5522.1 | 5327 |

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| EXAMINER | |
|---|---|
| LI, QIAN JANICE | |
| ART UNIT | PAPER NUMBER |
| 1633 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/23/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/003,669 | BROYLES ET AL. | |
| | Examiner | Art Unit | |
| | Q. Janice Li, M.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12/18/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,19,22,24,25,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,19,22,24,25,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The response and amendment filed 12/18/2006 are acknowledged. Claims 1, 19, 22, 24, 25, 27 have been amended. Claim 28 is newly submitted. Claims 1, 19, 22, 24, 25, 27, 28 are under current examination.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 28 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record as applied to original claims 1, 3, 11-13, 19, 23 (see Office actions mailed 7/17/2003 and 1/14/2004).

Claim 28 recites administering to a subject a therapeutically effective dosage of a ferritin-H *derivative*. However, the specification as filed fails to provide an adequate written description for the recited derivatives, particularly a genus of derivatives capable of binding to the promoter of a human β globin gene at –148 to –153 bp from the transcription start site.

To the extent that the derivatives used in the claimed method are not adequately described in the instant disclosure, claim 28 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described, which is not conventional in the art.

Claims 1, 19, 24, 25, and 27 stand rejected and claim 28 is newly rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record and following.

In the Remarks filed 12/12/06, applicants reiterated theoretical basis and outline of the claimed invention. In response, as indicated in the previous Office actions, the matters at issue here is not whether the underlying theories are sound, but how to translate the theories into clinical benefit, to a therapeutic process for treating sickle cell disease. As has been discussed extensively before, years of medical research and clinical studies have proven again and again that bring a laboratory observation to a practical clinical use is a complex process and requires more than a sound theory. In the instant case, although applicant has shown in cell culture that supplying a nucleic acid expressing ferritin-H suppresses expression of the β-globin gene, and leading to renewed expression of γ-globin, hence contemplates that replacing β-globin with γ-globin would result in suppression of sickle cell disease. In response, such extrapolation

oversimplifies the process of treating a complicated disease as discussed in record previously. Particularly considering the evidence that contacting ferritin-H with globin-producing cells *in vitro* and *in vivo* leads to the suppression of bone marrow erythroid precursor cells (*Broxmeyer et al*, PNAS 1991;88:770-4). Thus the overall effect of administering FtH on treating sickle cell disease is unpredictable, and would require undue experimentation.

Applicant submitted a publication describing research done in the 1980's using 5-azacytidine to reactivate the production of hemoglobin after birth, which ameliorates symptoms of sickle cell disease. In response, 5-azacytidine is not FtH, the two are different chemical compounds and have distinct modes of operation, and thus the experimentation on 5-azacytidine is insufficient to support the enablement of FtH for treating the sickle cell disease.

As to the argument that ferritin-H is not present in adult red blood cells, the applicant cited *Harrison PM et al.* (1996) to support their view and to argue that "*serum ferritin contains only ferritin-L subunits and has no FtH subunits whatsoever*" (page 6 of the remark).

In response, it is noted *Harrison* reference does not support the applicant's assertion that ferritin-H is not present in adult red blood cells. To the contrary, *Harrison et al.* teaches the subunit compositions of the red blood cell ferritin contains **22** heavy chain subunits (FtH), and 2 light chain subunits (figure 1). Indeed figure 1 also shows that serum ferritin does not contain heavy chain subunit, however, since the essential element in a blood transfusion unit is not serum, but red blood cells, blood transfusion

would supply ferritin-H.

Therefore, in view of the state of the art, the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is now claimed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 22 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Broxmeyer et al* (PNAS 1991;88:770-4).

*Broxmeyer et al* teach a pharmaceutical composition comprising a recombinant human heavy-chain ferritin (column 2, page 770), and administering such *in vitro* and *in vivo* to bone marrow cells (page 771) or mice (page 773). Accordingly, *Broxmeyer et al* anticipate instant claims.

In the remarks, the applicant asserts the ferritin used by *Broxmeyer et al* is not a pharmaceutical composition, comprising a therapeutically effective amount of ferritin-H capable of binding to the promoter of a human β globin gene at –148 to –153 bp from the transcription start site.

The argument has been fully considered but found not persuasive. This is because there is no dosing limitation in *Broxmeyer et al.* Further, "a pharmaceutical composition" merely describes an intended use. It is noted that the use of a product for

a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand-alone. The MPEP states, "in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

As to the capability of promoter binding, it is the intrinsic property of ferritin-H. MPEP 2112.01 instructs that "PRODUCTS OF IDENTICAL CHEMICAL COMPOSITION CAN NOT HAVE MUTUALLY EXCLUSIVE PROPERTIES.' A CHEMICAL COMPOSITION AND ITS PROPERTIES ARE INSEPARABLE". THEREFORE, IF THE PRIOR ART TEACHES THE IDENTICAL CHEMICAL STRUCTURE, THE PROPERTIES APPLICANT DISCLOSES AND/OR CLAIMS ARE NECESSARILY PRESENT. *IN RE* SPADA, 911 F.2D 705, 15 USPQ2D 1655, 1658 (FED. CIR. 1990).

Accordingly, the rejection stands.

Claims 1, 19, 22, 27 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Adams et al* (New Eng J Med 1998;39:5-11), and as evidenced by *Files et al* (J Pediatric Hematol Oncol 2002;24:284-90) and *Sowemimo-Coker* (Transfus Med Rev 2002 Jan;16:46-60).

The claims are drawn to a method for treating sickle cell disease in humans, comprising exposing a globin-producing cell to a ferritin-H such that the globin-producing cell absorbs the ferritin-H.

*Adams et al* teach preventing a first stroke of sickle cell anemia in children by red blood transfusion (See particularly abstract and § Methods), wherein the red blood cells comprises ferritin-H. Although not relied upon, *Files et al* teach that for years red blood transfusion has been used to correct anemia in sickle cell patients, and serum ferritin

levels increased lineally with cumulative transfusion volume in humans (e.g. abstract, § Result), indicating transfusion of red blood cell indeed supplement FtH. *Sowemimo-Coker* teaches that the lysis of RBC (hemolysis) does occur during processing, storage and transport (abstract), and thus, the nuclear ferritin-H is present in RBC transfusion unit, and RBC transfusion supplies FtH via more than one means. Instant claims are broadly drawn to any means of exposing exogenous ferritin-H to globin-producing cells, which encompasses the red blood transfusion. Accordingly, *Adams et al* anticipate instant claims.

In the remarks, the applicant argues on the basis that transfused adult blood contains only minute amounts of ferritin-H, below therapeutic amount.

In response, as indicated in figure 1 of the *Harrison* reference (1996, IDS), a red blood cell contains much more heavy chain ferritin subunits than light chain subunits ($H_{22}L_2$), and blood transfusion is not about transferring serum but red blood cells. Thus, the FtH should be abundant in the blood.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

## ***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on 571-272-0739. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has

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For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

**Q. JANICE LI, M.D.**
**PRIMARY EXAMINER**

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

*QJL*
March 19, 2007